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Cross-Reactive T Cell Responses to Dengue Viral Antigens and the Cytokine Profile Among Dengue Fever and Dengue Haemorrhagic Fever Patients in Malaysia

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Dengue virus infections are a major cause of morbidity and mortality in tropical and sub-tropical areas in the world. The attempts to develop effective vaccines have been hampered by the lack of understanding of the pathogenesis of the disease and the absence of suitable experimental models for the dengue viral infection.

The objective of this study is to identify and investigate potential T cell epitopes and to investigate the cytokines and chemokines profile in dengue fever (DF) and dengue haemorrhagic fever (DHF) patients in Malaysia. The magnitude of T cell responses and the involvement of cytokines and chemokines molecules have been reported to correlate with dengue disease severity. Sixty Malaysian adults with dengue viral infections were investigated for their dengue virus-specific T cell responses to 32 peptides antigens from the structural and non-structural regions from dengue virus isolate. Seventeen different individual peptides from C, E, NS2B, NS3, NS4A, NS4B and NS5 were found to evoke positive gamma interferon responses by using enzyme-linked immunospot (ELISPOT) assay in thirteen patients with DF and DHF with the range of 50-700 SFU/10^6 PBMC. NS3 and predominantly $NS3_{422-431}$ peptide were found to be important T-cell targets. The ELISPOT analyses also revealed high frequencies of T cells that recognize both serotype-specific and cross-reactive dengue virus antigens in patients with DHF. The results strongly support the presence of high frequencies of activated $CD8^+$ T cell in patient with DHF with the highest reactivity being seen to NS3 region. Preliminary data on the level of cytokines indicate a probable role for IL-1ra, IL-6, IL-12 and TNF-α in DF, and IL-1ra, IL-4, IL-6, IL-8, IL-9, IL-10, TNF-alpha and IFN-gamma in DHF patients. Chemokines, MCP-1, Eotaxin, Rantes, IL-8 and IP-10 were also detected at increased levels in both DF and DHF patients as compared to controls. Currently an attempt is being made to collect serial daily samples prior to vascular leakage for cytokine analysis.